REMARKS/ARGUMENTS

Applicants appreciate the efforts of the Examiner to expedite this application and thank the Examiner for making the Office Action of December 24, 2003 non-Final.

Applicants further thank the Examiner for reconsidering and withdrawing the prior grounds of rejection in view of our Amendment of November 12, 2003.

Status of the Claims

Claims 78-97, 99, 102-104, 113, 114, 116, 121-124, 127, 128, 136, 140, 142 and 143 are pending and continue to be presented for examination.

Claims 78-99, 102-104, 116, 121-123, 127, 128, 136, 142 and 143 stand rejected for an alleged wont of enablement pursuant to 35 U.S.C. §112, first paragraph.

Claims 113, 114, 124 and 140 stand objected to as depending from a non-allowed claim. Applicants thank the Examiner for pointing out the subject matter presently deemed to be in condition for allowance.

Applicants respond to the above rejections below.

Response to the Rejection of Claims 78-99, 102-104, 116, 121-123, 127, 128, 136, 142 and 143 under 35 U.S.C. §112, First Paragraph

The Subject Matter at Issue.

The Examiner alleges the scope of the first peptidyl subject matter of the base claims lacks enablement with respect to variants thereof which are shorter than about 40 amino acids in length and/or have about one or two amino acid substitutions or deletions within the first peptidyl sequence as set forth in the base claims.

Standard of Review

As noted by the Examiner, whether undue experimentation[1] is required to practice an invention is typically determined by evaluating: (i) the relative skill of those in the art; (ii) the nature of the invention; (iii) the breadth of the claims; (iv) the amount of guidance presented; (v) the presence of working examples; (vi) the state of the art; (vii) the predictability of the art; and (viii) the quantity of experimentation necessary. *Ex parte Forman*, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. & Inter. 1986), *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). Applicants address each of these factors and the Examiner's concerns as to each in turn.

i. Relative Skill of those in the Art.

Applicants submit that the relative skill of those in the art of recombinant proteins and peptide manufacture is high. Typically, such practitioners have doctoral degrees in the relevant fields. The competence of such practitioners is evidenced in U.S. Patent No. 5,719,021 to Inouye and Inouye et al. Enzymes 45:314-321 (1991)(both references cited by the Examiner) and the other references already of record.

ii. Nature of the Invention.

The field of the invention is in the pharmaceutical arts and more particularly the *manufacture* of correctly folded recombinant peptides. In the pharmaceutical arts, it is routine to screen a large number of agents for their biological activity. Herein, the relevant biological activity is an intramolecular chaperone activity. The candidate first peptidyl fragments can be screened *in vitro* for their ability to increase the yield of a correctly folded recombinant insulin peptide. Insulin is one of the oldest and most studied peptide hormones.

[1] That some experimentation may be necessary to identify operative species does not constitute a lack of enablement. As the Federal Circuit has stated, "the key word is 'undue', not 'experimentation' " in determining whether pending claims are enabled. *In re: Wands*, 8 U.S.P.Q.2d at 1405 (Fed. Cir. 1988). Indeed, a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance for practicing the invention.

iii. Breadth of the Claims.

Base claim 78 recites in part "a first peptidyl fragment of from 20 amino acids in length to 92 amino acids in length and having an amino acid sequence which is identical to an N-terminal amino acid sequence of SEQ ID NO: 2 of the same length as the first peptidyl fragment or having an amino acid sequence which differs by one or two residues from the N-terminal sequence of SEQ ID NO:2 of the same length." Thus, the first peptidyl subject matter is constrained to first peptidyl fragments having from 20 to 92 amino acids and varying in amino acid sequence from a corresponding sequence set forth in SEQ ID NO:2 by only 0, 1, or 2 residues.

iv. Amount of Guidance Presented.

Applicants teach all the methods required to practice the claimed subject matter. The specification teaches methods of making such subject matter at pp. 22-23, of testing such first peptidyl fragments for their intramolecular chaperone activity in Section 4.5 beginning on p. 28) and exemplifies such in the Examples. The specification teaches how to obtain, purify and characterize a resulting correctly folded human insulin in Sections 5.5 through 5.6, respectively. Moreover, as recited in the MPEP §2164.01 "A patent need not teach, and preferably omits, what is well known in the art." Inouye (see U.S. Patent No. 5,719,021; already of record) also more generally teaches standard methods which one of ordinary skill in the art could readily adapt in order to practice the invention.

v. Presence of Working Examples.

The specification provides working examples based upon using a 49 amino acid long intramolecular chaperone first peptidyl sequence and a correctly folded insulin precursor of the claims. The inventor's affidavit evidenced the suitability of a 40-mer first peptidyl fragment and the unsuitability of an 18-mer first peptidyl fragment. Thus, the ability to make and identify suitable and unsuitable first peptidyl fragments is demonstrated.

vi. State of the Art.

The art of varying making and testing variant intramolecular chaperone peptides is substantially more advanced than the Office Action sets forth. Inouye in U.S. Patent No. 5,719,021 helps to illustrate the advanced state of the intramolecular chaperone art generally. This reference concerns subtilisin, a very large enzymatically active protein whose folding is facilitated by an intramolecular chaperone prosequence. Inouye teaches how to identify the functional domains of an intramolecular chaperone necessary for folding, and exemplifies the mutational method for generating and testing intramolecular chaperone variant polypeptides. Inouye is interested in mapping the domains of the intramolecular chaperone important to intramolecular chaperone function. Inouye gives emphasis to the effect of amino acid substitutions and deletions on the functionality of intramolecular chaperones not to show operable mutations are improbable or uncommon as the Office Action would have it, but rather to prove that the N-terminal portion of the pro-subtilisin operates as an intramolecular chaperone by disrupting its function. He also uses the mutations to indicate the location of the domains of the intramolecular chaperone peptidyl fragment that are important to its operability. In contrast to the Examiner's use of the reference, Inouye also unequivocally sets forth that the there are a great many mutations that would preserve the intramolecular chaperone function. In fact, Inouye states at col. 5, third full paragraph:

> The identification method can be so conducted to determine one or more functional domains responsible for folding the inactive polypeptide into a biochemically active conformation. Substitutions of functionally equivalent amino acids can be performed in the identified domain(s) and the resulting peptide tested in accordance with the identification method. Peptides can thus be made which are still effective to activate the polypeptide but contain no amino acid residue(s) which is identical to that of the native pro-sequence.

Indeed, the Inouye patent issued with the following base claim which is considerably broader with respect to both its intramolecular chaperone subject matter and its folded peptide subject matter:

> 1. An in vitro method to restore or increase the natural biological activity of a target polypeptide, which is normally expressed containing a prosequence, which target polypeptide is biologically inactive or has decreased natural biological activity due to improper folding of the polypeptide, which method comprises reacting intermolecularly in a buffered ionic aqueous medium, thereby favoring hydrophobic interaction, an exogenous activating peptide with the target polypeptide, *wherein the activating peptide has the amino acid sequence of the prosequence of the target polypeptide or of a polypeptide which has the same function as the target polypeptide and which is similar in amino acid sequence to the target polypeptide,* whereby the activating peptide promotes refolding the target polypeptide into its biologically active conformation.

[Italics added for emphasis.] Independent claims 15 and 22 of the Inouye reference are also similarly broad with respect to their intramolecular chaperone subject matter.

(vii) Predictability of the Art.

The Examiner paraphrases MPEP §2112.02-2112.03) to support the contention that "characterizing a new property in a known product is highly unpredictable." However, MPEP §2112 concerns nonobviousness; and therefore any such rule would apply to the nonobviousness assessment and *not* the enablement assessment. Moreover, such a general principle of nonobviousness would stand without reference to *any* field of art whereas the "predictability of the art" is predicated upon the particular art(s) in which the invention lies.

In contrast, MPEP §2164.03 titled "Relationship Between Predictability in the Art and the Enablement Requirement" sets forth that "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the *disclosed* or known results to the claimed invention." [italics added for emphasis] (see p. 2100-182, second full paragraph first column). Applicants have *disclosed* the new property of the first peptidyl fragment as being a suitable intramolecular chaperone for folding an insulin precursor fragment. In view of the above-discussed state of the art, Applicants submit that one of ordinary skill in the art could extrapolate the disclosed results concerning the intramolecular chaperone properties of the first peptidyl fragments as set forth in the base claims of the instant application.

In support of the contention that the relevant art is unpredictable, the Examiner cites both Inouye references (i.e., U.S. Patent No. 5,719,021 and Inouye, Enzymes 45:314-321 (1991)) as disclosing inoperable subject matter. Both Inouye references can be cited to illustrate mutations and truncations in an intramolecular chaperone that can eliminate its intramolecular chaperone activity with respect to the target peptide. The Examiner cites Inouye as disclosing that deleting the first 15 or 43 amino acids of their intramolecular chaperone eliminates the chaperone function. The Examiner also cites Inouye as disclosing that many amino acid sequence substitutions within the intramolecular chaperone can eliminate its chaperone activity. However, Applicants note that according to the MPEP §2164.08, the standard of patentability is not whether any inoperable subject falls within the scope of a claim:

> **2164.08(b) Inoperative Subject Matter**
> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling).

The test of enablement is rather on whether one of ordinary skill in the art would have to perform *undue* experimentation in order to practice the claimed invention. In this regard, Inouye does not stand for the proposition that there are no operable intramolecular chaperone variants in his system. While Inouye may have focused on inoperable subject matter so as to prove the role of the intramolecular chaperone and to identify its critical domains, Inouye actually taught that there were many operable intramolecular chaperone variants for subtilisin:

> In studies with subtilisin (but not limited thereto), pro-peptides which are synthetic as opposed to the native pro-sequence, have been shown to contribute to the folding of the peptide to an active conformation by an intermolecular reaction. The amino acid constitution and/or sequence of the amino acid residues of the activating peptide need not be the same as that of the native pro-sequence. It is generally sufficient that it be in part the same as that of the native pro-sequence in that it contains one or more of the identified

> functional domains to cause the inactive polypeptide to be activated biochemically.

(Inouye U.S. Patent No. 5,719,021 at col. 5, 2nd full paragraph). Indeed, Inouye pursued and was granted correspondingly broad claims as discussed above.

Inouye went much further to show that one can even obtain compensating amino acid substitutions at a second site in the polypeptide amino acid portion of the *target* which offset a mutation in the intramolecular chaperone portion of the molecule so as to restore both intramolecular chaperone activity and the correct folding. Thus, Inouye demonstrates that a very high state of the art exists in so far as he was able to modify both the intramolecular chaperone portion and the target to provide a coordinated set of mutations.

In short, Inouye simply does not support the proposition the Examiner would find there.

viii. Quantity of Experimentation Necessary.

The field of the invention is the pharmaceutical arts. A great deal of experimentation is quite routine in this field. It is a field which is largely devoted to the screening and testing of a large number of candidate compounds, compositions and treatments in model systems[2]. Indeed, Wands itself is evidence that a great deal of screening activity if routine is no bar to enablement. In addition, clinical testing is not required to demonstrate the clinical utility of the product. Correctly folded insulins are among the oldest and best known of the peptide hormones.

In fact, very little additional experimentation would be required to practice other embodiments of the invention. With respect to variant first peptidyl fragments of less than 48 amino acids in length, the Applicants have filed a declaration setting forth that a 40 mer is an

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[2] Indeed, The Federal Circuit has held that if a specification teaches one embodiment and sets forth a method for determining dose/response, the experimentation required to determine a dose/response curve is not undue, even if the studies proved to cost approximately $50,000 and took 6-12 months to accomplish. *United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988).

effective intramolecular chaperone for an insulin precursor and that an 18-mer is inoperable. To avoid any inoperable truncations occurring over the 22 amino acid span of the difference between these two lengths, one of ordinary skill in the art would only need to make and test only a handful of such variants to determine the minimum length needed for operability. With respect to variant first peptidyl subject matter having one or two amino acid substitutions, such subject matter is readily ascertainable by one of ordinary skill in the art and could be readily achieved by substitution of one like amino acid for another (acid for acid, base for base, hydrophobic for hydrophobic, etc.). As discussed above, Inouye teaches that one of ordinary skill in the art could readily obtain *operable* limited variants of such intramolecular chaperone sequences.

Overall Summary of the Wands Analysis

Here,

(i) the relative skill and experience of those in the relevant fields of recombinant protein expression and peptide synthesis is high.

(ii) the nature of the invention is in the manufacture of correctly folded insulin peptides using intramolecular chaperones; the contested subject matter concerns amino acid sequence and length variants of intramolecular chaperones.

(iii) the breadth of the claims is fully commensurate with the specification disclosure, in particular, in view of the previous amendments, a greatly reduced number of possible variants of first peptidyl fragments are involved;

(iv) the specification provides adequate guidance for all manipulations required to practice the invention;

(v) the specification provides working examples; the declaration sets forth a 40 amino acid long first peptidyl fragment is operable and that an 18 amino acid long first peptidyl fragment was inoperative.

(vi) the state of the art is high as exemplified by the work of Inouye.

(vii) the art is sufficiently predictable such that one of ordinary skill in the art could practice subject matter within the scope of the claimed subject matter without undue experimentation; here, the Applicants have readily shown two embodiments of such are operable.

(viii) while the field of art is one in which a great deal of experimentation is routinely performed by a person of ordinary skill in the art, in fact relatively little additional research would be required to practice the invention.

In view of the above, Applicants believe that one of ordinary skill in the art could readily practice the invention as claimed using an amount of experimentation which would be clearly routine in the art. Applicants therefore request that the above rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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